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10/556,123	11/09/2005	Steffen Panzner	56362.4	4731

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/556,123	PANZNER ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 19-37* is/are pending in the application.

4a) Of the above claim(s) *2,23-34 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-6,19-22,35 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6 and 19-37 are pending in the present application.

Applicant's election with traverse of Group I, drawn to a depot system containing one or more protein or peptide active substances, a drug comprising the same depot system and **the first method** of using the same depot system by injecting the depot system subcutaneously or intramuscularly, in the reply filed on 2/20/2000 is acknowledged. Applicant further elected the following species: (a) DPPC as a species of saturated synthetic phosphatidyl choline; (b) DC-Chol as a species of a cationic lipid; and (c) LHRH agonists as a species of protein and peptide active substances.

With respect to the Group restriction, the traversal is on the ground(s) that there will not be a serious burden on the Examiner because the classification and the field of search are so closely related and similar. With respect to the species restriction, the traversal is that the Examiner has not suggested or set forth the number of species is unreasonable, and that the relative small amount of species that do not require a burdensome classification, bibliographic, manual and computer search for the Examiner.

These are not found persuasive for the reasons discussed below.

With respect to the Group restriction, it is noted that liposomes having specific recited components in specific recited mole –percentages can be used to deliver active substances other than peptides and proteins such as DNA, RNA, oligonucleotides (e.g., small interfering RNA, decoy oligonucleotides, aptamers, spieglemers) or small organic molecules which are different structurally and chemically one from the others, and

methods of using these different encapsulated therapeutic drugs would require different technical considerations for attaining the desired end-results. Therefore, it would be a burden for the examiner **to search and examine** all of the claims in a single application. The examiner notes that the entire set of claims 26-34 is improperly dependent on the independent claim 1 because at least oligonucleotide is not a protein or a peptide active substance. It is also noted that the instant specification is the 371 application of PCT/DE04/00998, and reasons for the lack of unity of invention according to Rule 13.1 PCT have been clearly set forth in the Office action mailed on 12/20/07 (pages 2-8).

With respect to the species restriction, it is a burden for the examiner to examine and search **7** different possible species combinations of saturated synthetic phosphatidyl cholines as written, **5** different species of cationic lipids as components of the liposomes, along with **at least 5** different proteins and peptide active subtances (e.g., LHRH agonists, GnRH analogs, insulin, heparin and antigen fragments for vaccination) within the elected Group, let alone for all the claims pending in the present application.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 26-34 and 36 were withdrawn from further consideration because they are directed to non-elected inventions. Additionally, claims 2, 23-25 were withdrawn from further consideration because they are directed to non-elected species.

Therefore, claims 1, 3-6, 19-22, 35 and 37 are examined on the merits herein with the above elected species.

Claim Objections

Claim 1 is objected to because terms such as "DMPC", "DPPC", "DSPC", "DC-Chol", "DAC-Chol", "DMTAP", "DPTAP" and "DOTAP" should be spelled out in full at the first occurrence of the terms. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-6, 19-22, 35 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al. (US 5,770,222) in view of Gregoriadis et al. (US 7,008,791).

Unger et al already disclosed a drug delivery system comprising gas-filled liposomes having encapsulated therein a therapeutic drug, wherein at least about 75% or at least about 90% of the therapeutic drug and gas content of the liposomes remain with the liposomes because of their impermeability until they reach the internal region of a patient to be targeted and ultrasound is applied (see at least the abstract; Summary of the Invention; col. 4, line 61 continues to line 27 of col. 5; col. 7, lines 8-13, lines 24-32). Unger et al also taught that **the materials which may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation**, and the lipid in the gas-filled liposomes may be in the form of a single bilayer or a multilamellar bilayer and that utilized lipids to create liposome microspheres include and not limited to: lipids such as dimyristoylphosphatidylcholine (DMPC), dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine (DSPC), cholesterol, cholesterol sulfate and cholesterol hemisuccinate and if desired a variety of cationic lipids such as DOTMA, DOTAP can also be used, wherein in general the molar ratio of cationic lipid to non-cationic lipid in the liposome may be between 2:1 to 1:10 (col. 7, line 42 continues to line 53 of col. 8). Unger et al also disclosed that any of a variety of therapeutics may be encapsulated in

the liposomes, including leuprolide acetate, growth hormones, peptides such as manganese super oxide dismutase, enzymes such as alkaline phosphatase, monoclonal antibody, and genetic materials including nucleic acids, DNA and RNA (col. 9, line 30 continues to line 34 of col. 11). Unger et al further disclosed that for intravascular application, the liposome microspheres can be about 30 nm in mean outside diameter (col. 15, lines 12-13); for providing therapeutic delivery to organs liposome micropheres between about 30 nanometers and about 100 nanometers in mean outside diameter can be used (col. 15, lines 14-18). Unger et al further taught that the drug delivery system can be administered into a patient using various routes of administration, including subcutaneously, intramuscularly among others (col. 16, lines 31-44).

Unger et al do not teach specifically the preparation of a liposome comprising saturated synthetic phosphatidyl cholines selected from one or more from the group consisting of DMPC, DPPC and DSPC; cholesterol and/or derivatives with a percentage ranging from about 35 to about 50 mole-%, cationic lipids selected from the group of DC-Chol, DAC-Chol, DMTAP, DPTAP and DOTAP with a percentage ranging from about 5 to 20 mole-%, and one or more selected from the group consisting of protein and peptide active substances.

However, at the effective filing date of the present application Gregoriadis et al already disclosed at least a liposome preparation comprising at least a cationic compound such as DOTAP or DC-Chol (col. 2, line 65 continues to line 9 of col. 3; col. 3, lines 45-61), at least one zwitterionic phospholipid such as DPPC and DSPC (col. 3,

line 62 continues to line 15 of col. 4), and cholesterol, wherein the amount of cationic compound is preferably in the range of 5 to 50% of the total moles of liposome forming components, preferably in the range 10 to 25% mole and the cholesterol is in amounts up to 50% by weight (col. 4, line 16 continues to line 26) to entrap a DNA encoding an antigen (see at least the abstract). Gregoriadis et al further taught that the product liposomes may be multilamellar or unilamellar vesicles, and the small vesicles have average diameters in the range 200 to 300 nm (col. 4, lines 27-38). Exemplified liposome preparations include a liposome comprising 32 umoles of DSPC, 16 umoles of cholesterol and 8 umole of DOTAP (example 1, preparation 3); 32 umoles of DSPC, 16 umoles of cholesterol and 8 umoles of DC-Chol col. 8, lines 20-23). Gregoriadis et al further taught that the liposome compositions have been found to be resistant to bile salts and this correlates with stability at least in the GI tract (col. 5, lines 39-41).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the teachings of Unger et al by also utilizing a liposome preparation having liposomal components in the ratios taught by Gregoriadis et al above to encapsulate and deliver a therapeutic drug to a patient.

An ordinary skilled artisan would have been motivated to carry out the above modification because the liposome preparation taught by Gregoriadis et al has been demonstrated to be stable and suitable at least for as an oral-based DNA vaccine. It is further noted that Unger et al taught explicitly that the materials which may be utilized in preparing liposomes include any of the materials or combinations thereof known to those skilled in the art as suitable for liposome preparation.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Unger et al. and Gregoriadis et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN, Ph.D./
Primary Examiner, Art Unit 1633